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FROM THE DEPARTMENT OF CANCER EPIDEMIOLOGY, RADIUMHEMMET, THE DEPARTMENT OF EPIDEMIOLOGY, INSTITUTE OF ENVIRONMENTAL MEDICINE, KAROLINSKA INSTITUTE, STOCKHOLM, AND THE DEPARTMENT OF LUNG MEDICINE, HUDDINGE HOSPITAL, HUDDINGE, SWEDEN.

SMOKING AND PASSIVE SMOKING IN RELATION TO LUNG CANCER IN WOMEN

C. SVENSSON, G. PERSHAGEN and J. KLOMINEK

Abstract

In a population based case-control study the association between female lung cancer and some possible etiological agents was investigated; 210 incident cases in Stockholm county, Sweden, and 209 age-matched population controls were interviewed about their exposure experiences according to a structured questionnaire. A strong association between smoking habits and lung cancer risk was found for all histological subgroups. Relative risks for those who had smoked daily during at least one year ranged between 3.1 for adenocarcinoma to 33.7 for small cell carcinoma in a comparison with never-smokers. All histological types showed strong dose–response relationships for average daily cigarette consumption, duration of smoking, and cumulative smoking. There was no consistent effect of parental smoking on the lung cancer risk in smokers. Only 38 cases had never been regular smokers and the risk estimates for exposure to environmental tobacco smoke were inconclusive. The high relative risks of small cell and squamous cell carcinoma associated with smoking may have implications for risk assessments regarding passive smoking.

Key words: Lung carcinoma, smoking, environmental tobacco smoke, case-control.

Carcinoma of the bronchi and lungs (lung cancer) is a common and highly lethal malignant disease. The dominating role of smoking as causative factor is established through numerous studies. The incidence is generally much higher among men, but in the USA lung cancer is now replacing breast cancer as the leading cause of cancer mortality among women (1). Among Swedish women the trend for annual increase of lung cancer is second only to malignant melanoma of the skin (2).

Many studies have shown that adenocarcinoma constitutes a greater proportion of the lung cancer incidence in females than in males (3). The difference can partly be explained by differences in smoking habits between the genders, but there are some indications that a similar pattern can be seen in non-smokers (4, 5).

During the last few years several studies have indicated that 'passive smoking' or exposure to environmental tobacco smoke (ETS) may be of etiological importance. The findings have recently been evaluated (6). Most of the studies have focussed on the effects of ETS exposure during adulthood, but some data suggest an effect of childhood exposure both in smokers and non-smokers (7, 8).

To further investigate the effects on women of smoking and other possible etiological factors for lung cancer, such as ETS and radon exposure in the home, and possible protective effects of some dietary components, we performed a population based case-control study. The first part of the study, addressing the risks associated with smoking and ETS, is presented in this paper.

Material and Methods

The study included Swedish-speaking women living in Stockholm county between 1983 and 1986. Persons in the county with suspected or newly detected lung cancer are as a rule referred to one of three clinical departments of lung medicine (Karolinska, Huddinge, and Södersjukhuset), or to the Department of Thoracic Surgery (Karo-

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linska) for further investigation and/or treatment. To be included in the present study, the subjects should be in a physical and mental condition that allowed an interview lasting between one half to one hour.

Suspected and confirmed cases were interviewed in the hospital wards. For inclusion in the study the diagnosis should be confirmed microscopically or by unambiguous chest radiograms in conjunction with a typical clinical course. The majority of interviews were made before the diagnosis was confirmed. When a case was confirmed and included in the study, a population control born on the same day was chosen at random from the population register in Stockholm county. If she could not be traced or refused to participate, she was replaced by another woman, who was selected and contacted in the same manner. The controls were interviewed by the same persons that interviewed the cases. The control interviews were made during a personal visit (58%) or by telephone.

A hospital control group was also included in some of the analyses pertaining to ETS-exposure. This group was selected among those patients with suspected lung cancer who were interviewed, but for whom the subsequent investigation ruled out this diagnosis.

The cases and hospital controls were interviewed during September 1983–December 1985. The last population control was interviewed one year later. The time lag between interviews of cases and population controls was mainly caused by the interval between admittance of a patient to a clinic and definite confirmation or rejection of the preliminary diagnosis. Eighty-six percent of the study subjects were interviewed by two physicians (CS and JK). The remaining subjects were interviewed by two other physicians.

A structured questionnaire was used for the interviews. It contained questions about frequency of consumption of foodstuffs rich in vitamin A, carotenoids, and vitamin C, exposure to ETS, smoking, and data on all dwellings in which a subject had lived for more than two years continuously. Exposure to ETS was assessed through questions about domestic exposure during childhood as well as domestic and work environment exposure during adult life. The criterion for being classified as a smoker was that the subject should have smoked daily for at least one year.

Statistical evaluation was made with the computer program EPILOG (9). Relative risks (rate ratios) were mainly estimated by stratified analyses with the extension for trend of the Mantel-Haenszel procedure (10, 11). In the trend analysis the exposures were scored 1, 2, 3, etc. In the matched analyses the exact method for computing confidence intervals (CI) described by Miettinen was used (12). In the unmatched analyses Cornfield's method was used (13). For some of the analyses multiple logistic regression models were used as well (14). Significance intervals presented in the article are two-sided and 95% CI are used throughout.

Results

The study finally included 210 cases and 209 population controls. In addition, 191 interviewed patients were shown not to have lung cancer. For 9 patients primary lung cancer could neither be confirmed nor excluded. Seven subjects refused interview and 5 could not be interviewed because of their medical condition.

One hundred and seventy-five (84%) of the population controls were first hand choices. One control did not have a corresponding case, since the case had to be excluded during the analysis, when an autopsy revealed primary carcinoma of the colon with pulmonary metastases and not primary lung cancer. For two cases no controls willing to be interviewed were found.

Table 1 shows the microscopical classification of the cases. All but two were histologically or cytologically confirmed. In one of these an autopsy showed characteristic macroscopical changes of malignant nature, but unfortunately a microscopical investigation was not made. Adenocarcinoma was most common and constituted approximately one-third of the cases. The age distribution was similar in the different histological groups.

Table 2 displays the diagnoses for the non-lung cancer patients along with their smoking status. Malignant disease other than lung cancer was the most common cause and constituted approximately one-fourth of this group of patients. An additional 17 patients in this group had a malignant disease although not directly associated with their respiratory ailments and consequently not the reason for their hospitalization. Table 2 also shows that the proportion of smokers among the population controls was smaller than for the non-lung cancer patients.

Smoking. All analyses pertaining to smoking were made using the population controls only. The relative risk for lung cancer for those who had ever smoked vs. never-smokers was calculated both in a matched analysis and in an unmatched analysis adjusted for age. The two methods yielded similar results, e.g. the risk estimate for all lung cancers was 5.8 (CI: 3.4–10.3) in the matched analysis and 6.4 (CI: 4.0–10.5) in the unmatched. The highest risk was seen for small cell cancer (33.7, unmatched) and the lowest for adenocarcinoma (3.1, unmatched). The mean age for the cases, who were never-smokers, was higher than for those who had ever smoked (66.3 vs. 61.7, $p=0.009$).

Table 3 shows the dose-response relationships for different types of lung cancer with average daily cigarette consumption as exposure variable. Subjects who had stopped smoking more than two years prior to the interview (for population controls two years before the interview of the corresponding case) were classified as ex-smokers. Small cell and squamous cell carcinomas showed the strongest trend of increasing relative risk with increasing smoking intensity. For some of the estimates the CI was very wide because of the small number of never-smokers among the cases, especially among those

Table 1

Lung cancer cases among women in Stockholm county according to histological type of tumor and diagnostic verification

	Histol. evidence		Cytol. evidence		No microsc. evidence		Total		Mean age (years)
	n	%	n	%	n	%	n	%	
All cases	148	70.5	60	28.6	2	1.0	210	100.0	62.5
Squamous cell	41	77.4	12	22.6	0	0.0	53	25.2	63.7
Small cell	30	66.7	15	33.3	0	0.0	45	21.4	62.6
Adeno	55	76.4	17	23.6	0	0.0	72	34.3	61.6
Other	22	55.0	16	40.0	2	5.0	40	19.0	62.3

Table 2

Diagnoses and smoking among female non-lung cancer patients interviewed at departments for pulmonary diseases in Stockholm county as well as proportion of smokers among population controls

Diagnosis	n	%	Smokers %
Malignant tumor	47	24.6	59.6
Breast	13	6.8	46.2
Gynecological	11	5.8	54.5
Pneumonia or other respiratory infection	35	18.3	54.3
Unspecified pulmonary infiltration	23	12.0	65.2
Benign tumor or cyst	22	11.5	40.9
Pleuritis	8	4.2	50.0
Tuberculosis	5	2.6	60.0
Sarcoidosis	5	2.6	20.0
Haemoptysis	5	2.6	100.0
Chronic bronchitis	5	2.6	100.0
Bronchiectasis	4	2.1	75.0
Atelectasis	4	2.1	25.0
Other specified diagnosis	24	12.6	67.0
Unspecified diagnosis	4	2.1	50.0
Total	191		58.1
Population controls	209		42.6

with squamous or small cell cancer. Nevertheless, the lower limit of the CI was 2.9 and 6.9 respectively for the lowest smoking category within these groups of cancer. Only one control belonged to the highest exposure category, why the risk estimates for this category became very imprecise.

Average daily consumption of cigarettes was highly correlated to cumulated smoking (r=0.90, CI: 0.88–0.92) and to duration of the smoking habit (r=0.73, CI: 0.68–0.77). As a consequence of the high correlations the dose–response relationships were similar for these exposure measures.

The influence of the age at debut of daily smoking on relative risk is shown in Table 4. The risks are adjusted for duration of smoking. No statistically significant association could be found between smoking debut and risk although almost all point estimates of relative risk were higher for those starting before 25 years of age than after. Analyses were also made with simultaneous adjustments for age and intensity of smoking. The results were similar in both types of analysis, although the risk estimates were somewhat higher when the latter type of standardization was used. This could be expected as persons with an early debut also had a higher cumulated exposure within each age stratum. Other age stratifications were analysed, but the results were similar to those presented.

The effect of smoking cessation on relative risk of lung cancer is shown in Table 5. Few subjects, especially among the cases, with an average daily consumption of more than 10 cigarettes had ceased to smoke. The data indicated a considerable decrease in risk already within 10 years of smoking cessation compared to continued smoking. There seemed to be a stronger effect of smoking cessation for squamous and small cell carcinomas than for the other histological types.

Environmental tobacco smoke. Risk estimates of lung cancer associated with ETS were mainly calculated for cases and controls who had never been daily smokers, but for exposure to ETS during childhood calculations were also made for smokers. To increase power, the risk estimates presented for never-smokers were calculated with an expanded control group consisting of population controls and those non-lung cancer patients, who did not have any malignancy. The estimates arrived at when using only the population controls were quite similar. The carcinoids and the microscopically unconfirmed cases were excluded from the risk calculations pertaining to ETS.

Table 6 shows estimates of relative risk for smokers associated with exposure to ETS from the parents. Subjects with a smoking father only, were classified as exposed to low levels while subjects with a smoking mother were classified as exposed to high levels regardless of the smoking status of the father. No significantly increased relative risk was seen in any of the exposure groups.

Table 3

Relative risk (RR) for lung cancer among women in Stockholm county in relation to average daily cigarette consumption[1]

	Never-smokers	Ex-smokers		Current smokers						p for trend[2]
	n	n	RR (95% CI)	>0–10 cig/day		>10–20 cig/day		>20 cig/day		
				n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)[3]	
All cases	38	30	2.6 (1.4–5.1)	42	4.6 (2.5–9.3)	81	12.6 (6.5–25.2)	19	59.0 (7.6–)	$<1.4\times10^{-22}$
Squamous cell	5	6	4.0 (1.0–16.9)	10	9.7 (2.9–45.9)	28	36.2 (12.0–168.9)	4	96.0 (6.9–)	$<3.8\times10^{-16}$
Small cell	2	5	9.1 (1.4–69.7)	13	33.7 (6.9–265.3)	20	72.1 (11.9–452.6)	5	215.8 (18.3–)	$<1.8\times10^{-16}$
Adeno	22	12	1.8 (0.8–4.3)	12	2.2 (1.0–5.8)	22	5.4 (2.4–13.2)	4	19.7 (1.7–)	$<1.7\times10^{-7}$
Other	9	7	2.5 (0.8–8.1)	7	3.6 (1.1–13.4)	11	7.5 (2.2–24.3)	6	82.5 (7.6–)	$<8.0\times10^{-9}$
Controls	120	36		30		22		1		

[1] The estimates are adjusted for age. Subjects who had stopped smoking more than 2 years before the interview (for controls 2 years before the interview of the matched case) are classified as ex-smokers.
[2] Ex-smokers not included in calculations of linear trend. The exposures were scored 1, 2, 3 and 4.
[3] Upper confidence intervals not given because of imprecision of estimates due to the small number of individuals in the high exposure stratum.

Table 4

Relative risk (RR) for lung cancer among women in Stockholm county associated with age at debute of daily smoking[1]

	>25 years	19–25 years		–18 years		p for trend[2]
	n	n	RR (95% CI)	n	RR (95% CI)	
All cases	32	58	2.0 (0.8–5.3)	52	1.2 (0.5–2.8)	0.9
Squamous cell	9	18	2.0 (0.6–7.3)	15	1.1 (0.3–3.8)	0.9
Small cell	7	18	2.2 (0.6–8.4)	13	1.3 (0.4–4.9)	0.9
Adeno	10	11	1.6 (0.4–6.0)	17	1.3 (0.4–4.4)	0.6
Other	6	11	2.2 (0.5–9.9)	7	1.0 (0.2–4.2)	0.7
Controls	18	14		21		

[1] Stratified analysis adjusted for duration of smoking. Subjects who had stopped smoking more than 2 years before the interview (for controls 2 years before the interview of the matched case) are excluded.
[2] The exposures were scored 1, 2 and 3.

although all risk estimates exceeded 1.0 in women with smoking mothers.

In never-smokers, adenocarcinoma constituted the dominating histological group with 22 (57.9%) of the total of 38 carcinomas. There were only 5 squamous cell and 2 small cell carcinomas, making specific analyses of these histological groups unfeasible.

Table 7 shows risk estimates for different ETS exposure variables among never-smokers. Most of the point estimates of the relative risk were greater than unity but the CI were wide due to the small number of cases. There were no significant trends. Multiple regression analysis yielded risk estimates very similar to those presented in the table.

There was a significantly increased risk of being exposed to ETS in the home, if the subject herself was a

Table 5

Relative risk (RR) for lung cancer among women in Stockholm county associated with smoking cessation (sc) compared to current smoking (0–2 years after cessation)[1]

	Current smoking n	3–10 years since cessation		>10 years since cessation		p for trend[2]
		n	RR (95% CI)	n	RR (95% CI)	
All cases	142	16	0.6 (0.2–1.4)	14	0.3 (0.1–0.6)	0.0004
Squamous cell	42	5	0.5 (0.1–1.6)	1	0.0 (0.0–0.4)	0.0006
Small cell	38	2	0.3 (0.0–1.3)	3	0.2 (0.0–0.7)	0.001
Adeno	38	5	0.5 (0.1–1.7)	7	0.5 (0.2–1.5)	0.06
Other	24	4	0.7 (0.2–3.2)	3	0.4 (0.1–1.6)	0.08
Controls	52	13		24		

[1] Stratified analysis adjusted for age and average daily cigarette consumption.
[2] The exposures were scored 1, 2 and 3.

Table 6

Relative risk (RR) for lung cancer among ever smoking women in Stockholm county in relation to parental smoking during the first decade of life[1]

	Unexposed n	Father smoker		Mother smoker[2]		p for trend[3]
		n	RR (95% CI)	n	RR (95% CI)	
All cases	94	57	0.8 (0.3–1.4)	19	1.8 (0.5–7.0)	0.9
Squamous cell	27	17	0.7 (0.3–1.7)	4	1.3 (0.2–8.8)	0.6
Small cell	25	13	0.7 (0.3–1.8)	5	2.1 (0.3–14.0)	1.0
Adeno	23	19	1.1 (0.5–2.5)	8	3.0 (0.6–21.6)	0.3
Other	19	8	0.4 (0.1–1.3)	2	1.1 (0.0–20.0)	0.08
Controls	45	39		5		

[1] Stratified analysis adjusted for age and average daily cigarette consumption.
[2] Regardless of smoking habits of the father.
[3] The exposures were scored 1, 2 and 3.

smoker. The point estimate for cases was 4.0 (CI: 1.7–9.3) and for controls 3.0 (CI: 1.5–6.2). For controls there was also a significantly increased 'risk' of being exposed to ETS on the job if the subject had ever smoked (RR 1.9, CI: 1.0–3.7). For cases the corresponding point estimate was 1.1 (CI: 0.5–2.6).

Discussion

All subgroups of lung cancer were strongly associated with smoking. Due to the small number of never-smokers among the cases, especially among squamous and small cell cancers, and of heavy smokers among the controls, the confidence intervals were wide. The magnitudes of the risk estimates were greater than, but not incompatible with, results from previously published studies on female lung cancer (15–18).

Contrary to previous studies (15, 17, 19) no clear association between early smoking debut and risk was seen, although most of the point estimates were greater than unity when smoking debut after age 25 was used as reference category. In light of the clear dose–response rela-

Table 7.

Relative risk (RR) for lung cancer among never smoking women in Stockholm county in relation to different measures of exposure to ETS[1]

	Cases	Controls	RR	95% CI
Exposure from the parents[2]				
Unexposed	19	98	1.0	
Father smoker	12	71	0.9	0.4–2.3
Mother smoker	3	5	3.3	0.5–18.8
		(p for trend[3]: 0.6)		
Exposure as adult				
Unexposed	10	60	1.0	
At home or at work	17	90	1.2	0.4–2.9
At home and at work	7	24	2.1	0.6–8.1
		(p for trend[3]: 0.4)		
Lifetime exposure				
Unexposed	7	35	1.0	
As child[2] or adult	15	88	1.4	0.2–2.5
As child[2] and adult	12	51	1.9	0.2–3.7
		(p for trend[3]: 0.5)		

[1] Stratified analysis adjusted for age.
[2] Age 0–9 years.
[3] The exposures were scored 1, 2 and 3.

tionships in the other studies as well as in studies on men, the present findings were unexpected. A possible explanation could be that those who started to smoke at a younger age inhaled less deeply or that they to a greater extent smoked cigarettes with filter tips. The observed decrease in the relative risk of lung cancer after smoking cessation is in agreement with previous observations (16, 18, 20).

Approximately one-third of all cases were classified as adenocarcinoma. Among the never-smokers adenocarcinoma constituted almost 60% of the cases. Among the current smokers the corresponding figure was 27%. The proportion of adenocarcinoma among the never-smokers is in good agreement with several previous studies on female lung cancer (5, 16, 21–23).

The results pertaining to ETS in the present study were not conclusive. The small number of never-smokers among the cases could be one important reason. It should be noted, however, that most of the point estimates of relative risk were greater than unity which agree with results from previous studies on ETS exposure and with risk estimates concerning active smoking (6, 24).

To reliably estimate the risk associated with ETS, it is essential to identify a sufficient number of never-smokers. In the present study, only 38 of the 210 cases had never been daily smokers. Four of these were excluded from the calculations of risks associated with ETS, since they had carcinoids or tumors which were not confirmed microscopically. A post hoc calculation of power for detecting a 50% excess risk associated with exposure to ETS in the home, showed that it was in fact only about 10%.

For detecting small risks, it is essential to minimize misclassification of exposure. The variables characterizing exposure to ETS used in this study may not be optimal in this respect. Both intensity and temporal aspects of the exposure are probably of importance for the outcome. It is very difficult, however, to retrospectively quantify ETS exposure. The tolerance for tobacco smoke differs between individuals, and it is not improbable that this can influence their exposure estimates. If such individual information bias exists, it is uncertain whether it leads to non-differential or systematic misclassification. There are also difficulties involved in assessing the relative importance of domestic exposure compared to exposure in the work environment.

The high risks found for smokers with a low consumption in this study, and particularly for squamous and small cell carcinomas, have implications for the assessment of lung cancer risks associated with ETS. On one hand, they suggest that relative risks of 3 or even higher for squamous and small cell carcinomas in heavily exposed individuals may not be unreasonable. On the other hand, they make control of confounding by smoking a critical issue. A poor control of confounding would be expected to primarily give rise to increased risks of these histological types.

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Request for reprints: Dr Christer Svensson, Department of Epidemiology, Institute of Environmental Medicine, Karolinska Institute, P.O. Box 60208, S-104 01 Stockholm, Sweden.

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